Stable isotope studies of nicotine kinetics and bioavailability

The stable isotope-labeled compound 3′,3′-dideuteronicotine was used to investigate the disposition kinetics of nicotine in smokers, the systemic absorption of nicotine from cigarette smoke, and the bioavailability of nicotine ingested as oral capsules. Blood levels of labeled nicotine could be measured for 9 hours after a 30-minute intravenous infusion. Analysis of disposition kinetics in 10 healthy men revealed a multiexponential decline after the end of an infusion, with an elimination half-life averaging 203 minutes. This half-life was longer than that previously reported, indicating the presence of a shallow elimination phase. Plasma clearance averaged 14.6 ml/min/kg. The average intake of nicotine per cigarette was 2.29 mg. A cigarette smoke–monitoring system that directly measured particulate matter in smoke was evaluated in these subjects. Total particulate matter, number of puffs on the cigarette, total puff volume, and time of puffing correlated with the intake of nicotine from smoking. The oral bioavailability of nicotine averaged 44%. This bioavailability is higher than expected based on the systemic clearance of nicotine and suggests that there may be significant extrahepatic metabolism of nicotine. (CLIN PHARMACOL THER 1991;49:270-7.)

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Cigarette smoking is addicting, and nicotine is the dependence-producing constituent of tobacco.[1] Pharmaceutical preparations of nicotine are employed as adjuncts to smoking-cessation therapy and may also be of use in treating medical illnesses such as Alzheimer's disease.[2,3] Central to our understanding of nicotine dependence and the rational use of nicotine as a medication is an understanding of its disposition kinetics and bioavailability from different routes of exposure.

Because nicotine is a noxious drug in most people who do not use tobacco, most studies of the pharmacokinetics of nicotine have been performed in tobacco users. Such studies are typically performed after a period of tobacco abstinence, at which time levels of nicotine in the blood have fallen.[4,5] However, even after overnight abstinence from tobacco, significant levels of nicotine persist, for which mathematic correction is required in performing pharmacokinetic computations after known doses of nicotine. In addition, there are potential problems with contamination of reagents or glassware with nicotine, which is present in significant amounts in the environment because of the widespread use of tobacco. Background levels of nicotine reduce the accuracy of nicotine measurements in biologic fluids at very low concentrations.

The use of stable isotope-labeled drugs allows pharmacokinetic studies to be performed in the presence of unlabeled drug. With a mass spectrometer, the labeled and unlabeled drug can be distinguished from one another, and their concentrations can be determined simultaneously. In the case of nicotine, the labeled drug is not found in the environment, allowing concentrations of the drug administered by infusion to be measured at lower levels.

We report here the use of 3′,3′-dideuteronicotine (nicotine-d_2) to investigate the disposition kinetics of nicotine in smokers and its application in the measure-

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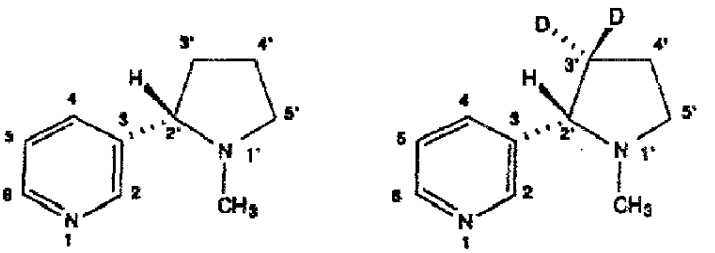

Structures of nicotine and 3',3'-dideuteronicotine.

ment of the bioavailability of nicotine inhaled from cigarette smoke and ingested as oral capsules. We also describe the use of an instrumental cigarette smoke monitor and its validation as a method of estimating human smoke exposure.

METHODS

Subjects. Ten healthy men, 24 to 48 years of age, who were regular cigarette smokers were the subjects for the study. They smoked an average of 33½ cigarettes per day (range, 15 to 50), with an average U.S. Federal Trade Commission (FTC) smoking machine yield of 1.1 (SD, 0.2) mg nicotine and 17.5 (3.9) mg tar. Subjects were highly dependent on cigarettes based on Fagerstrom score (average 7.3 of a possible score of 11)[6] and admission blood concentration of cotinine (328 ng/ml; SD 144 ng/ml; range 111 to 589 ng/ml). Results of biochemical tests of liver and kidney function were within normal limits for all subjects.

Experimental protocol. Subjects were hospitalized at the General Clinical Research Center at San Francisco General Hospital Medical Center for 3 days. The first day was for acclimatization to the ward and to enforce no smoking after 10 PM. On the morning of the second day, after overnight abstinence from cigarette smoking and in a fasting state, intravenous catheters were placed in the antecubital vein of one arm for infusion of nicotine and into the forearm vein of the other arm for blood sampling. Subjects were asked to smoke one (five subjects) or two (five subjects) of their usual brand of cigarette. The cigarettes were smoked with a cigarette holder attached to the smoke-monitor system described below. Subjects were instructed to smoke the cigarette as naturally as possible. Forty minutes later, after cigarette smoking had been completed, an intravenous infusion of nicotine-d_2, 2 μg base/kg/min, was administered for 30 minutes. The infusion was administered after completion of smoking so that the exogenously administered nicotine would not influence smoking behavior, which is determined, at least in part, by the level of nicotine in the body. Frequent blood samples were taken before, during, and after smoking and before, during, and after the infusion as follows: 0, 4, 8, 12, 16, 20, 24, 28, 32, 40, 50, 60, 70, 85, 90, 120, 150, 180, 240, 300, 360, 480, 600, and 720 minutes. Further smoking was not allowed until the time of the last blood sample.

On the morning of the third day, again after overnight abstinence from tobacco and food, subjects were given a capsule containing 3 mg (seven subjects), 4 mg (two subjects), or 6 mg (one subject) nicotine base as the bitartrate salt. The 3 mg dose was selected as the one expected to deliver about 1 mg to the systemic circulation, similar to the dose absorbed from smoking a cigarette. The 4 and 6 mg doses were intended to explore subjects' subjective responses to higher doses. Blood samples were collected at 0, 15, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, 360, and 420 minutes. The intravenous infusion was not repeated. Subjects were not permitted to smoke until the completion of blood sampling.

Deuterium-labeled nicotine. A nicotine analog in which two deuterium atoms are located on the 3′ position of the pyrrolidine ring (structure) was synthesized. The site of labeling was chosen because it is remote from the two major sites of nicotine metabolism, which include formation of cotinine (oxidized at the 5′ position) and nicotine 1′-*N*-oxide (addition of oxygen to the pyrrolidine nitrogen).[7] Previous studies have demonstrated that the disposition kinetics of nicotine-d_2 and natural nicotine are similar.[8] This deuterium-labeled compound was synthesized as described previously,[9] converted to the bitartrate salt, and purified by

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recrystallization from aqueous alcohol. A solution of nicotine bitartrate for injection was made up in saline solution, sterilized by autoclaving, and aliquoted into sealed vials under a nitrogen atmosphere.

Cigarette smoke monitor. The instrumental cigarette smoke monitor system was designed at Oak Ridge National Laboratory to measure directly smoke constituents generated by smokers. The system, a computerized version[10] of a system described in detail elsewhere,[11] consists of a cigarette holder, a flow measurement system, a smoke concentration detector, and a multiplier/integrator electronics package. Smoke flow and smoke concentration are determined simultaneously; the signals are multiplied electronically, and the product signal is integrated. The integrator response was proportional to the mass of smoke particulates passing through the holder. The data output of the cigarette smoke monitor system consists of volume, duration, and total particulate matter (TPM) for each puff and time between puffs.

Chemical analyses. Plasma concentrations of nicotine and nicotine-d_2 were measured by selected ion monitoring GC/MS, with nicotine-d_4 used as an internal standard.[8] Although the limit of sensitivity of the assay is 0.1 ng/ml, the limit of quantitation (as supported by available quality control data) was 1.0 ng/ml. Therefore values below 1 ng/ml were excluded from pharmacokinetic analysis. Plasma concentrations of cotinine on admission to the study were measured by gas-liquid chromatography,[12] modified for use of a capillary column.

Data analysis. Plasma nicotine-d_2 concentrations during and after intravenous infusion were fitted to one-, two-, and three-compartment body models by expended least squares regression (MKMODEL).[13] The two- and three-compartment model fits of the data were markedly superior to the one-compartment model, so the one-compartment data are not presented. The three-compartment model appeared to be superior to the two-compartment model by a combination of visual inspection and the Schwartz criteria,[14] in four of the 10 subjects. However, only two subjects had an adequate three-compartment fit based on the confidence intervals of the standard error of the estimated parameters. Because the difference in the quality of fit between two- and three-compartment models for these two subjects was marginal, the results of the two-compartment fitting are presented for all subjects.

Clearance (CL) and steady-state volume of distribution (V_{SS}) were calculated by two different methods. First, CL was estimated as an unknown parameter in the two-compartment fit, which is analogous to the use of the integral of the equation to the fitted concentrations to calculate the area under the plasma concentration–time curve (AUC). CL was also calculated as dose/area under the plasma nicotine-d_2 concentration–time curve ($AUC_{nic\text{-}d_2}$). $AUC_{nic\text{-}d_2}$ was computed by the linear trapezoidal rule for ascending concentrations and the log trapezoidal rule for descending concentrations.[15] The terminal area of the $AUC_{nic\text{-}d_2}$ was calculated as the last nicotine-d_2 concentration/k, where k is the terminal slope of the nicotine-d_2 concentration–time curve, estimated by linear regression of the final five concentration-time data pairs.

With the parameters estimated for the two-compartment fitting, V_{SS} was calculated as follows:

$$V_{SS} = V_C(1 + k_{12}/k_{21})$$

in which V_C is the volume of the central compartment and k_{12} and k_{21} are the intercompartmental rate constants. V_{SS} was also calculated with the area under the moment curve (AUMC), where the terminal area of $AUC_{nic\text{-}d_2}$ and $AUMC_{nic\text{-}d_2}$ was calculated, with k estimated from the last five concentration-time pairs mentioned above. Computation of the AUMC included correction for the duration of the infusion.

The dose of nicotine (D) systemically absorbed from cigarette smoking or oral capsules was determined with the area under the plasma nicotine concentration–time curve for the natural (unlabeled) nicotine (AUC_{nic}) and the clearance of labeled nicotine ($Cl_{nic\text{-}d_2}$) as $D = AUC_{nic} \times Cl_{nic\text{-}d_2}$. The terminal portion of the area under the unlabeled plasma nicotine concentration–time curve was estimated from the last plasma nicotine concentration/k, where k was taken from the terminal portion of the nicotine-d_2 concentration–time curve. The AUC_{nic} was corrected for the predosing concentration by subtracting C_O/k, where C_O was the plasma level of natural nicotine before smoking or ingesting the capsule. Plasma concentrations of nicotine after smoking and oral nicotine were analyzed for up to 300 and 420 minutes, respectively, after which time the concentrations fell below the limit of quantitation.

The relationship between smoking parameters computed by the cigarette smoke monitor and absolute availability of nicotine was analyzed by linear regression.

RESULTS

Plasma concentrations of nicotine-d_2 could be measured accurately for up to 540 minutes after the end of nicotine infusion (Fig. 1). The shape of the postinfu-

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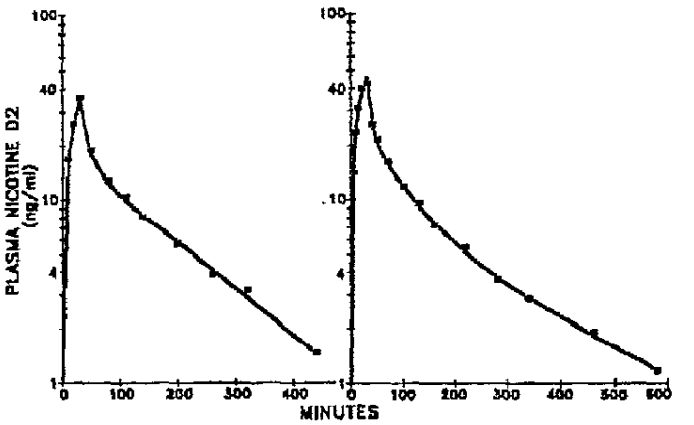

Fig. 1. Plasma nicotine-d_2 concentration-time curves during and after intravenous infusion of 2 μg/kg/min for 30 minutes in two subjects. The subject shown in the **left panel** (subject 4) shows a biexponential decline in plasma levels, whereas the subject in the **right panel** (subject 7) shows an apparent triexponential decline. The *solid line* indicates the fit based on two- or three-compartment body model equations for subjects 4 and 7, respectively (MKMODEL).

Table I. Pharmacokinetics of nicotine-d_2

Subject No.	*Body weight (kg)*	*CL (L/min)**	*CL (L/min)†*	*V_C (L)**	*V_{SS} (L)**	*V_{SS} (L)†*	*$t_{1/2\alpha}$ (min)**	*$t_{1/2\beta}$ (min)**	*$t_{1/2\beta}$ (min)†*
1	81.7	1.07	1.05	62	200	212	9.0	155	185
2	68.3	1.20	1.05	82	202	291	15.2	149	309
3	89.9	1.06	1.07	58	196	206	7.9	151	182
4	71.1	1.21	1.20	67	174	175	8.9	119	124
5	82.8	1.15	1.04	62	202	269	8.8	148	275
6	71.8	1.11	1.05	16	169	211	1.0	116	173
7	68.1	0.96	0.94	34	135	159	6.2	121	170
8	78.2	1.19	1.21	153	242	309	21.3	157	271
9	75.0	0.96	1.01	20	176	213	2.2	148	195
10	84.4	1.46	1.40	27	269	261	0.8	136	149
Mean ± SD	77.1 ± 7.5	1.14 ± 0.14	1.10 ± 0.13	58 ± 40	196 ± 38	230 ± 50	8.1 ± 6.4	140 ± 16	203 ± 61

CL, Clearance; V_C, volume of the central compartment; V_{ss}, steady-state volume of distribution; $t_{1/2\alpha}$, distribution half-life; $t_{1/2\beta}$, elimination half-life.
*Parameter determined by two-compartment fitting procedure.
†Parameter determined by noncompartmental method.

sion plasma concentration–time curve was in all cases multiphasic. In most cases the curve was well described by a biexponential equation, although in two cases the curve seemed to be described better by a triexponential equation (Fig. 1).

Pharmacokinetic parameters are presented for the two-compartment model fit and the noncompartmental analysis, with the half-life ($t_{1/2}$) determined from the last five data points (spanning the terminal 420 minutes) (Table 1). CL averaged 1.12 L/min (14.6 ml/min/kg) and was nearly identical as estimated by the two methods. CL values were remarkably similar among subjects, with a coefficient of variation of only 12%. With the two-compartment body model, the $t_{1/2}$ values of the α and β phases averaged 8.1 and 140 minutes, respectively. The elimination $t_{1/2}$ derived from the last five concentration points was consistently longer, averaging 203 minutes. V_{ss} was consistently larger with the noncompartmental method (mean, 203 L or 3.0 L/kg) compared with the two-compartment V_{ss} (140 L or 2.5 L/kg).

An example of plasma nicotine concentration–

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Table II. Cigarette smoking, puffing parameters, and bioavailability of inhaled and oral nicotine

Subject No.	*FTC nicotine yield (mg)*	*FTC tar yield (mg)*	*No. cigarettes smoked*	*Puffs/cigarette*	*Total puff vol/cigarette (ml)*	*Average puff volume (ml)*
1	0.7	10	2	7.5	460	61.6
2	1.3	23	2	9	436	48.4
3	1.0	16	2	8.5	372	43.6
4	1.1	17	2	10	424	42.1
5	1.3	23	2	14.5	588	40.6
6	1.2	17	1	11	721	65.6
7	1.4	21	1	9	329	36.6
8	1.0	16	1	12	630	52.5
9	1.1	16	1	16	596	37.3
10	1.0	16	1	14	744	53.2
Overall mean ± SD	1.1 ± 0.2	17.5 ± 3.9	—	11.1 ± 2.9	530 ± 146	48.1 ± 10.0

FTC, U.S. Federal Trade Commission; TPM, total particulate matter.

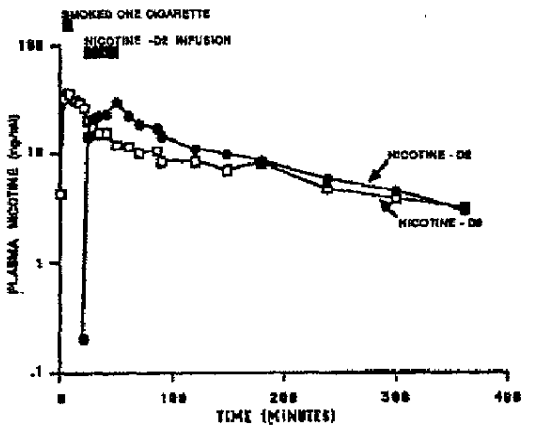

Fig. 2. Plasma concentrations of nicotine and nicotine-d_2 in a subject showing data for cigarette smoking and simultaneous infusion of nicotine-d_2. Note that nicotine-d_2 levels are shown only out to 360 minutes for sake of graphic clarity.

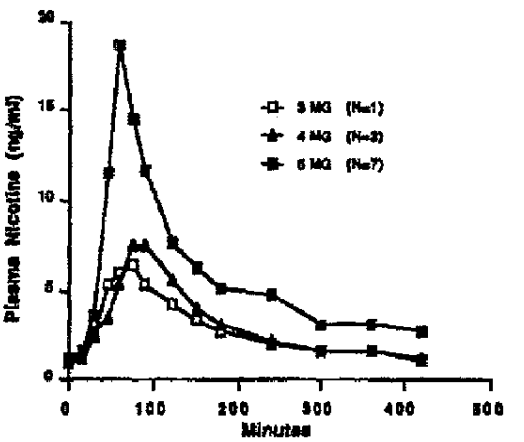

Fig. 3. Plasma concentrations of nicotine after ingestion of capsules containing nicotine bitartrate. Data represent a mean of seven subjects for the 3 mg nicotine base, two subjects for the 4 mg dose, and one subject for the 6 mg dose.

time curves after cigarette smoking and infusion of nicotine-d_2 is shown in Fig. 2. On average, the smokers systemically absorbed 2.29 mg nicotine/cigarette, with a range of 0.37 to 3.47 mg. These values were considerably higher than the machine-determined nicotine yields, and there was no correlation between the actual and machine-determined yields. Puffing parameters and TPM measured by the cigarette smoke dosimeter are shown in Table II. Considering all 10 subjects, there was a significant correlation only between nicotine intake per cigarette and TPM ($r = 0.72$; $p < 0.01$). However, excluding subject 9, who demonstrated an extraordinarily low nicotine intake compared to TPM (presumably as a result of puffing without inhaling), there were in the remaining group of nine subjects several significant correlations between nicotine intake per cigarette and smoke dosimeter–derived parameters: nicotine intake per cigarette versus number of puffs ($r = 0.88$; $p < 0.01$), versus total puff volume ($r = 0.76$; $p < 0.05$), versus total puffing time ($r = 0.75$; $p < 0.05$), and versus TPM ($r = 0.75$; $p < 0.05$).

It is noteworthy that comparing the average per-cigarette values for the five subjects who smoked one cigarette with the values for those subjects who smoked two cigarettes, the number of puffs (12.4 ver-

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Total puff duration/cigarette (sec)	*TPM (mg/cigarette)*	*Nicotine intake/ cigarette (mg)*	*Oral nicotine dose (mg)*	*Oral nicotine absorbed (mg)*	*Oral Bioavailability*
19.4	21.9	1.38	3	1.17	0.39
15.6	46.4	1.78	3	1.18	0.39
9.8	24.0	1.68	3	1.77	0.59
13.6	28.8	2.12	3	1.48	0.49
22.8	43.8	3.26	3	1.27	0.42
26.4	48.1	2.98	3	1.50	0.50
15.1	50.8	2.56	6	2.53	0.42
24.4	47.8	3.47	4	1.60	0.40
18.7	30.1	0.37	3	0.73	0.24
24.9	49.1	3.22	4	1.97	0.49
19.1 ± 5.5	39.1 ± 11.5	2.29 ± 1.00	—	—	0.44 ± 0.09

sus 9.9), total puff volume (604 versus 456 ml), total puffing time (21.9 versus 16.3 seconds). TPM (45.7 versus 35.0 mg), and nicotine intake (2.52 versus 2.05 mg) were greater when only one cigarette was smoked, although the differences were highly variable and were not statistically significant.

Oral nicotine was well tolerated by all subjects. Most were not aware of any pharmacologic effect. The subject who received the highest dose (6 mg) of nicotine complained of nausea and abdominal cramping that began about 30 minutes after ingesting the capsule and lasted for 60 minutes. Nicotine was absorbed quickly, with a peak level occurring at about 90 minutes (Fig. 3). The oral bioavailability averaged 44% (range, 24% to 59%) (Table II).

DISCUSSION

We demonstrate the use of stable isotope-labeled nicotine for studying the disposition kinetics and bioavailability of the drug. Plasma concentration curves for nicotine-d_2 were generally smooth, without the variability and persistent background levels of nicotine commonly seen after administration of natural nicotine. Blood levels could be followed with confidence for up to 9 hours after the end of the infusion, and no corrections for preinfusion plasma nicotine levels were necessary. The pharmacokinetic parameters derived from infusion of nicotine-d_2 are in general similar to those reported previously for natural nicotine.[4,5,16,17] However, one difference is noteworthy. It is apparent that, when nicotine levels are monitored for many hours, the elimination phase is multiexponential. With a two-compartment body model, the elimination $t_{1/2}$ was estimated to be 140 minutes, which is similar to those estimated in previous studies after infusion of natural nicotine or after cigarette smoking. However, the curves for most subjects were not perfectly fitted to a biexponential equation. According to model-independent methods, the terminal five plasma concentration data points, representing the last 7 hours, demonstrated a $t_{1/2}$ of 203 minutes. Including the terminal portion of the elimination phase in the clearance calculation does not appear to be important because the area included under that portion of the curve is small. However, the long elimination $t_{1/2}$ does indicate that the V_{ss} is somewhat larger than that estimated by the two-compartment body model. We suggest that future pharmacokinetic studies be analyzed by a noncompartmental approach and blood levels be followed for at least 9 hours after the end of administration for an accurate estimation of elimination $t_{1/2}$.

Stable isotopes are ideal for bioavailability studies in that an intravenous infusion of a known dose can be administered simultaneously with administration of the test drug formulation. In this study the formulation was cigarette smoke. The estimated systemic absorption of nicotine from cigarette smoking in this study averaged 2.3 mg, which is much higher than the average of 1 mg per cigarette derived from people smoking ad libitum throughout the day.[5,18] It is likely that the unusually high level of nicotine intake in our subjects reflects the fact that the subjects (who had not smoked for the previous 10 to 12 hours) knew that they could smoke only one or two cigarettes during the next 12 hours. When access to cigarettes is restricted, cigarette smokers [redacted] increase their per cigarette smoke intake by three- [redacted] or greater.[19] Presumably that is what was occurring in our cigarette-deprived volunteers, despite instructions to smoke naturally. In addition, our subjects smoked these cigarettes through a cigarette holder

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(part of the smoke dosimeter), which is an unnatural way to smoke and could have influenced smoking behavior and nicotine intake. Effects of tobacco abstinence, either before testing or anticipated after testing, and the use of cigarette holders on smoking behavior should be considered by other investigators.

The Oak Ridge National Laboratory cigarette smoke monitor was developed to measure directly the generation of particulate matter from a puff of a cigarette. Unlike the smoking machine (FTC method), which measures TPM derived from cigarettes smoked in a mechanical fashion, the smoke monitor can measure particulates generated by a person smoking a cigarette. This is important because the quantity and composition of tobacco smoke generated during cigarette smoking depend on the number of puffs, the size and velocity of the puff, and which part of the cigarette is being puffed.[20] The smoke monitor had been validated previously with a smoking machine[10] but not in people smoking cigarettes. We have confirmed a significant correlation between the number of puffs, total puff volume, and time of puffing with the systemic intake of nicotine per cigarette in smokers. Similar results have been reported by other investigators measuring the increment in plasma nicotine concentration after smoking a cigarette.[21-23] Our cigarette smoke monitor measures TPM directly, which in general is correlated with the delivery of nicotine.[24] We observed a moderate degree of correlation, with only 56% of the variance in nicotine intake accounted for by measurement of TPM. The failure to account for more of the variance is not surprising for two reasons. First, there are differences from brand to brand in tar/nicotine ratios, as seen in Table II. Second, the cigarette smoke monitor measures TPM only in what passes out of the cigarette; it does not measure how much the smoker actually inhales, which varies considerably from smoker to smoker and even from cigarette to cigarette.[25] Because most of the nicotine that is absorbed derives from inhaled smoke, delivery of particulates to the mouth is not expected to be a perfect indicator of the systemic absorption of nicotine. For example, one of the subjects with a high level of TPM measured by the smoke monitor absorbed very little nicotine systemically, presumably because he was a noninhaler.

Of note is that both the systemically absorbed dose of nicotine and the TPM measured by the smoke monitor were approximately twice that predicted by the FTC smoking machine (Table II). The similar proportional differences from the FTC values further support the validity of the TPM measurement with the smoke monitor.

Our subjects generally tolerated oral nicotine well, as has been reported by other investigators.[26] The oral bioavailability was adequate to achieve plasma levels of nicotine similar to those seen after cigarette smoking. However, because of the prolonged course of absorption (compared with smoking), the subjective effects were dissimilar to those of smoking. The one subject who had abdominal cramping after a 6 mg dose did not have especially high plasma levels of nicotine compared with those observed during cigarette smoking, suggesting that the abdominal symptoms represent a direct effect of nicotine on gastrointestinal smooth muscle. That oral nicotine in doses of 3 or 4 mg is well tolerated and achieves blood levels similar to those achieved by chewing nicotine gum suggests that oral nicotine could be employed as a method of nicotine substitution for smoking-cessation therapy.

Although there was considerable individual variability, the average oral bioavailability of 44% was higher than expected based on the CL of nicotine. If all of the nonrenal clearance (CL_{NR}) of nicotine were the result of hepatic metabolism, an oral bioavailability of 33% would be predicted. The CL_{NR} of our subjects is estimated to be about 1.0 L/min (based on the CL measurement and published data that indicate that renal clearance is 5% to 10% of CL when urine pH is uncontrolled[17]). Assuming that liver blood flow averages 1.5 L/min and all of the CL_{NR} is hepatic, a first-pass extraction of 67% is anticipated, which would correspond to an oral bioavailability of 33%. Our data indicating that oral bioavailability is 44% suggest that one or more of those assumptions is incorrect. Nicotine is known to be metabolized to some extent by the lung[27] and conceivably by other organs; perhaps such extrahepatic metabolism explains the higher than anticipated oral bioavailability.

In conclusion, we provide data on the use of 3',3'-dideuteronicotine to study the pharmacokinetics of nicotine in tobacco users and to determine the absolute availability of nicotine from tobacco smoke or other nicotine-delivery formulations. We suggest that the high degree of analytic sensitivity of the stable isotope method and the specificity of labeled nicotine such that there is no interference by background levels of nicotine provides superior-quality pharmacokinetic data compared with measurement of natural nicotine. The results indicate that some of the currently accepted pharmacokinetic parameters for nicotine need to be revised. The application of stable isotopes

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should provide a useful tool to examine factors that influence nicotine kinetics and metabolism in tobacco users and to conduct bioavailability studies for newly developed therapeutic nicotine-delivery systems.

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